UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,877	01/09/2002	Tapas Mukhopadhyay	INRP:095US 10200175	6285

7590 03/18/2005

FULBRIGHT & JAWORSKI L.L.P.
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/043,877	MUKHOPADHYAY ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-163,166,168 and 171-175* is/are pending in the application.

4a) Of the above claim(s) *4-8,11,30-74,78-82,107-160,163,166,168 and 171-175* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9,10,12-29,75-77,83-106,161,162 and 164* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendments filed on 11/29/2004 and 01/10/2004 in response to the previous Non-Final Office Action (06/28/2004) is acknowledged and has been entered. The Declaration under 37 C.F.R. 1.131 filed on 11/29/2004 is acknowledged and has been entered.

Claims 1-163, 166, 168 and 171-175 are currently pending.

Claims 4-8, 11, 30-74, 78-82, 107-160, 163, 166, 168, and 171-175 are withdrawn from consideration as being drawn to non-elected inventions and/or species.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All rejections and/or objections are withdrawn in view of applicant's amendments and declaration there to.

New Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 98 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "about" in Claim 98 is a relative term, which renders the claim indefinite. The term "about" is not defined by the claim and one of ordinary skill in the art would not be reasonably

apprised of the scope of the invention. In the instant case, about 0.1 mg/kg could imply 0.01mg/kg to 1.0 mg/kg.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 9-10, 12-22, 29, 75-76, 83-100 and 161-162 are rejected under 35 U.S.C. 102(e) as being anticipated by Camden (US 6,262,093, 1999).

(Note: Due to the indefiniteness of the claims as set forth above, about 0.1 mg/kg (Claim 98) will be interpreted for art purposes as being from 0.01mg/kg to 1.0 mg/kg.)

In the instant case, the claims are drawn to: (i) a method of inducing apoptosis in a cell expressing a tumor suppressor gene by administering an effective amount of benzimidazole to a cell, wherein the benzimidazole derivative has a general benzimidazole formula (claims 1-2); (ii) a method of treating a patient having cancer expressing a tumor suppressor gene by administering an effective amount of a benzimidazole derivative, wherein the benzimidazole derivative has a general formula (claims 75-76); and (iii) a method of treating a patient with a hyperproliferative disorder comprising administering an amount of a benzimidazole derivative effective to induce apoptosis, wherein the hyperproliferative disorder is cancer (claims 161-162). The methods of (i) and (ii) are further drawn to wherein: the dose for (i) is at least 0.05 μg/mL (claim 9) and for (ii) is about 0.1 mg/kg or 1.0 mg/kg for (claims 98-99); (b) the cell is a tumor cell is a lung tumor cell, a non-small cell lung carcinoma cell, a breast cell, or a sarcoma cell (claims 12, 15-18, 88-91) or is a multidurg resistant cancer cell (claims 13-14, 86-87); (c) the tumor suppressor gene is p53 (claims 19, 21, 29, 83, 85) or MDA-7 (claims 20 and 84) and is determined prior to inducing apoptosis (claims 22 and 100); and (d) the administration for method (ii) comprises intratumoral, systemic, oral, area local to a tumor, or regional to a tumor, wherein the administration is repeated at least once (claims 10, 92-97).

Camden teaches (column 11, line 69 to column 12, line 51) a method of inducing apoptosis in cancer cells expressing abnormal p53 by administering an effective amount of a benzimidazole derivative. The patent further teaches (column 12, line 52 to column 13, line 24) a method of treating a patient having cancer expressing abnormal p53 by administering an effective amount of a benzimidazole derivative to induce apoptosis. Moreover, Camden discloses (column 14, line 53 to column 24, line 31) a method of treating a patient with cancer comprising administering an effective amount of a benzimidazole derivative. With regards to the cancer, the patent teaches that cancer includes, but is not limited to, cancers of the breast, lung, non-small cell lung and sarcoma (column 3, lines 45-50) or cancer that has survived treatment with another anticancer agent (column 29, lines 9-13). Specifically, Camden discloses the apoptotic effect in cancer cells such as, for example, MCF7 breast cells both in vitro (column 12, lines 46-51) and in vivo (column 16, lines 48+). With regards to the cancer cells, the patent teaches (column 12, lines 46-51) that some of the cancer cell lines tested are known to express abnormal p53. With regards to administration, Camden provides that 1 to 1000 mg/kg of a benzimidazole derivative (column 5, line 58 to column 6, line 17) can be administered orally, by intravenous injection, by parental administration or by injection into or around the tumor (column 6, lines 26-43). In addition, Camden teaches that the compound can be administered as a single daily dose or repeated at least once (column 6, lines 18-25). Furthermore, the patent shows that even at a concentration less than 10 μg/mL, the benzimidazole derivatives were capable of inducing apoptosis in p53 abnormal cell lines (column 12, lines 46-51). Thus, while Camden does not characterize the breast cells as expressing the tumor suppressor gene MDA-7, the claimed functional limitation would be an inherent property of the referenced since the specification (page 14, lines 11-18) teaches that MDA-7 is expressed in human breast cancer cells. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 9-10, 12-29, 75-76, 83-106 and 161-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Perdoma *et al.* (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18).

Camden teaches as set forth above with regard to claims 1-2, 9-10, 12-22, 29, 75-76, 83-100 and 161-162, a method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative.

Camden does not teach determining the tumor suppressor status by way of Southern blotting, Northern blotting, PCR, ELISA or Western blotting (claims 23-28 and 101-106).

Perdoma *et al.* teach determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma *et al.* further teach that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering a benzimidazole derivative using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Camden teaches the selectivity in killing p53 abnormal cell lines versus cells expressing normal p53 (column 12, lines 52+), while Perdoma *et al.* teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdoma *et al.* teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

Claims 1-3, 9-10, 12-29, 75-77, 83-99 and 161-162 are rejected under 35 U.S.C. 103(a) as being unpatentable over Camden (US 6,262,093, 1999) in combination with Delatour *et al.* (IDS, Therapie 1976; 31 (4); 505-515).

Camden teaches as set forth above with regard to claims 1-2, 9-10, 12-22, 29, 75-76, 83-100 and 161-162, a method of treating cancer by inducing apoptosis to a cell expressing abnormal p53 comprising administering a benzimidazole derivative. Camden does not teach that the benzimidazole derivative is mebendazole (claim 3 and 77).

Delatour *et al.* teach the ebryotoxic and antimitotic properties of benzimidazole compounds (title). Specifically, the reference discloses that in mice with Ehrich carcinoma mebendazole inhibited tumor growth and increased survival time (abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include mebendazole as taught by Delatour *et al.* in the method taught by Camden. One would have been motivated to make these modifications because as evidenced by Delatour *et al.*, benzimidazole derivatives such as mebendazole have been shown to inhibit tumor growth. Thus, one of ordinary skill in the art would have a reasonable expectation of success that using mebenzdazole as taught by Delatour *et al* in the method taught by Camden, one would achieve an additional benzimidazole derivative that induces apoptosis in cells and tumors expressing abnormal p53.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

GARY NICKOL
PRIMARY EXAMINER